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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,592	NELSON ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *8-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 14-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group 1 in the reply filed on 3/22/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 8-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-28 are pending.

Claims 1-7 and 14-28 are under consideration.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The addresses of all three inventors have been altered, but the alterations are not initialed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-7, 14-23, and 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-7, 14-23, and 24-28 are indefinite in their recitation of "treating a subject". The specification defines "treating" in the paragraph bridging pages 5 and 6, stating that by treating "is meant that at least one symptom associated or caused by the state, disorder or disease is diminished or alleviated, or at least one benefit unexpected under the normal condition, is achieved." However, it is unclear what is referred to by "the state", or by "one benefit unexpected under the normal condition". What is expected, and what is unexpected? This renders the term "treating" indefinite such that one of skill in the art cannot know the metes and bounds of the claims.

Claim 4 and dependents 5-7 and 14-16 are indefinite because claim 4 recites "[t]he method of Claims 1-3" without proper antecedent basis. Each of claims 1-3 is drawn to a method, so claims 1-3 together are drawn to 3 methods, not to one method.

Claim 5 is indefinite because it is unclear if by "Pluronics (F68, P65, P84, F127, 25R2, and L62)" the scope of "Pluronics" is being limited to the parenthetically listed compounds, or whether these are only intended as examples of Pluronics. So, one of skill in the art cannot know the metes and bounds of the claims.

Claims 5-7 are also indefinite because they recite the trademark/trade names "Triton", "Pluronic", and/or "Tween". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex

parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe specific surfactants and, accordingly, the identification/description is indefinite. Evidence that these are trademarks comes from page 40, lines 11, 12, and 15 of Lemieux et al (WO 00/47186) of record.

Claim 7 is also indefinite because it is unclear what is intended by 0.03-0.07%. The claims do not specify how the concentration is calculated, i.e. w/w, w/v, v/v, etc. So one of skill in the art cannot know the metes and bounds of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 20, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 19 and 20 are drawn to methods of treating a subject with any acquired or genetic disorder which is diminished or eradicated after the treatment, wherein the treatment comprises administering to any site an effective amount of amount of at least one excipient and at least one nucleic acid to enhance expression of said nucleic acid in said subject. Claim 20 limits the scope of subjects to pigs. The claims recite no nexus between any nucleic acid and any disease or disorder.

Claim 23 further is drawn to a method of treating a pregnant pig by administering to any site an effective amount of amount of at least one excipient and at least one nucleic acid to enhance expression of said nucleic acid in said pig. The nucleic acid must be a plasmid encoding porcine erythropoietin (EPO), and the survival rate or viability of the offspring piglets must be increased.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the

problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. Rosenberg et al (Science 287 :1751, 2000) stated that "[a}t present the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy's leading proponents have given the field a positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." See first full paragraph. Juengst (BMJ 326: 1410, 2003) indicated that the effects of gene therapy on cells are often multiple and unpredictable. See title and last sentence of first full paragraph of column 2. In summary, it is clear that gene therapy is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date has fallen short of initial expectations due to inadequate delivery and expression systems, and the unpredictable and pleiotropic effects of gene insertion and/or expression.

Those of skill in the art at the time of the invention were aware of a variety of methods of delivering nucleic acids in vivo, including methods using excipients such as

surfactants (e.g. Tween 80, Triton X-100, and Pluronics) (see rejections under 35 USC 102 and 103 below. However, in view of the state of the art as summarized above, these methods were inadequate to provide gene delivery and expression sufficient to and predictably support therapeutic outcomes. Even if one could predictably and reliably deliver and obtain expression of genes encoding proteins such as EPO, there is no reason in the prior art of record to lead one of skill in the art to believe that delivery of EPO to a pregnant pig would increase the survival rate or viability of piglet offspring.

The specification provides working examples of transfection of swine muscle with a reporter gene. The specification as filed teaches no working example of diminishing or eradicating any genetic or acquired disorder. The specification provides no guidance as to what nucleic acids could be used to treat any specific genetic or acquired disorder.

While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identity of expressed gene products that can be used to diminish or eradicate an acquired or genetic disorder is not a minor detail that can be overlooked in the process of providing an enabling disclosure.

In view of the unpredictable nature of in vivo gene delivery and expression, the state of the art at the time of the invention, the lack of working examples in the specification, and the failure to provide any novel guidance as to how overcome the art recognized barriers to therapeutic gene delivery and expression, one of skill in the art would have to perform undue experimentation in order to use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 17, 18, 21, and 24-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemieux et al (WO 00/47186).

Lemieux taught intramuscular injection of compositions comprising a DNA expression vector and a surfactant such as a Pluronic, a Tween, or a Triton. See title;

abstract; page 38, line 25; and page 40, lines 11, 12, and 15. Organisms for injection include the pig. See page 47, lines 1-3; and page 98, lines 5-15. Pluronics for use include F68, P65, P84, F127, 25R2, and L62, see pages 27 and 28.

Claims 1-4, 17, 18, and 24-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrano et al (US Patent 5,739,118).

This rejection is made against the generic form of the claims, i.e. the form not limited to any specific class of excipients.

Carrano taught methods of genetic immunization comprising intramuscular injection of compositions comprising DNA and saponins or anionic lipids. See column 1, line 60; column 20, lines 20-22; and claim 4. Because of their amphiphilic nature, saponins and anionic lipids are considered to be surfactants.

Claims 3-5, 17, 21 and 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemieux et al (Gene Therapy 7: 986-991, 2000).

Lemieux taught intramuscular injection into a mouse of compositions comprising a DNA expression vector and a mixture of Pluronics L61 and F127. See abstract and e.g. page 990, column 2, first two full paragraphs.

Claims 3-7, 17, 21, 25, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al (US Patent 6,120,794).

Liu taught complexes of DNA and surfactant compositions and intramuscular injection of the complexes into humans. See column 4, lines 1-4; column 9, lines 37 and 38, and claim 11. Nonionic surfactants include Pluronics such as F68 and F127, Triton X-100, Tween 20, and Tween 80. See column 7. Liu taught one composition comprising 0.05% Tween 80 and DNA. See formulation #23 in table 3 (columns 15 and 16).

Claims 1-4, 17, 18, 21, 22, and 24-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Draghia-Akli et al (US 20040038918).

This rejection is made against the generic form of the claims, i.e. the form not limited to any specific class of excipients.

Draghia-Akli taught a method of injecting into the muscle of a pregnant sow a composition comprising a plasmid DNA expression construct encoding growth hormone releasing hormone. The construct can be formulated in any vehicle which delivers a nucleic acid into a cell or organism, including plasmids, liposomes or cationic lipids. See paragraph 55 at page 5. Liposome-forming lipids and cationic lipids are considered to be surfactants in view of their amphipathic characteristics. The vehicle can also include glutamic acid, which is considered to be an excipient that enhances transport of the nucleic acid across the membrane. See e.g. claims 12-15, and paragraph 127 at page 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 14-18, 21, and 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carrano et al (US Patent 5,739,118) in view of Atala et al (US 20020055702).

Carrano taught methods of genetic immunization comprising intramuscular or intradermal injection of compositions comprising DNA and saponins or anionic lipids or liposomes. See column 1, line 60; column 12, lines 39-45; and column 20, lines 20-22. Because of their amphiphilic nature, saponins, anionic lipids and liposome forming lipids are considered to be surfactants. The compositions can also comprise one or more genetic vaccine facilitators, such as the penetration enhancer DMSO at a concentration of about 20%. See column 18, lines 48-61; and column 19, lines 42-44.

Carrano does not teach SEPA.

Atala taught Sharpe taught that DMSOs and SEPAs were recognized in the art as skin penetration enhancers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use SEP instead of, or in addition to DMSO, because both compounds were recognized in the art as skin penetration enhancers, and so would function as genetic vaccine facilitators in the invention of Carrano. MPEP 2144.06 indicates that it

is prima facie obvious to substitute or combine equivalents known to be useful for the same purpose.

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carrano et al (US Patent 5,739,118) and Atala et al (US 20020055702) as applied to claims 1-4, 7, 14-18, 21, and 24-28 above, and further in view of Liu et al (US Patent 6,120,794).

The teachings or Carrano and Atala are summarized above, and can be combined to render obvious the use of one or both of DMSO and SEPA, and a surfactant, in intramuscularly or dermally applied genetic vaccines.

These references do not teach the use of Triton X-100, Pluronics, or Tweens.

Liu taught that surfactants Pluronics (e.g. F68 and F127), Triton X-100, Tween 20, and Tween 80 facilitate the delivery of nucleic acids to cells by intramuscular or dermal administration. See e.g. abstract; column 7; column 11, lines 24-32, and claim 19. Liu taught one composition comprising 0.05% Tween 80 and DNA. See formulation #23 in table 3 (columns 15 and 16).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use Pluronics (e.g. F68 and F127), Triton X-100, Tween 20, or Tween 80 in as a surfactant in the invention of Carrano as modified by Atala. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component

or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). It would have been obvious to use Tween 80 in the range of .03-.07 percent because Liu uses it in this range.

Claims 3, 5-7, 17, 18, 21, 22, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over (US 20040038918) in view of Liu et al (US Patent 6,120,794).

Draghia-Akli taught a method of injecting into the muscle of a pregnant sow a composition comprising a plasmid DNA expression construct encoding growth hormone releasing hormone. The construct can be formulated in any vehicle which delivers a nucleic acid into a cell or organism, including plasmids, liposomes or cationic lipids. See paragraph 55 at page 5. Liposome-forming lipids and cationic lipids are considered to be surfactants in view of their amphipathic characteristics. The vehicle can also include glutamic acid, which is considered to be an excipient that enhances transport of the nucleic acid across the membrane. See e.g. claims 12-15, and paragraph 127 at page 13.

Draghia-Akli did not teach the use of Triton X-100, Pluronics, or Tweens.

Liu taught that surfactants Pluronics (e.g. F68 and F127), Triton X-100, Tween 20, and Tween 80 facilitate the intramuscular delivery of nucleic acids to cells. See e.g. abstract; column 7; column 11, lines 24-32, and claim 19. Liu taught one composition

comprising 0.05% Tween 80 and DNA. See formulation #23 in table 3 (columns 15 and 16).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Draghia-Akli by using the surfactants of Liu, because Liu taught that the surfactants facilitated delivery of nucleic acids. It would have been obvious to use Tween 80 in the range of 0.03-0.07 percent because Liu uses it in this range.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635